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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
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EXAMINER	
REES, D	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 08/484,786	Applicant(s) Mach et al.
	Examiner Dianne Rees	Group Art Unit 1807

☒ Responsive to communication(s) filed on *Apr 21, 1997* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *16, 17, 20, and 23-48* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *16, 17, 20, and 23-48* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The Applicant's arguments filed 4/21/97 have been thoroughly reviewed. Rejections and/or objections not reiterated from the previous office action are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated. They constitute the complete set being presently applied to the present application. Response to applicant's arguments follow.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16,17,20, 23,24,26-37,40-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA sequences of defined sequence composition, does not reasonably provide enablement for sequences defined solely by the property of hybridization, as coding for unspecified potions of proteins, degenerate sequences,

or sequences defined as complementary where no specificity of hybridization is defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. .

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described in *In Re Colianni*, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in *Ex Parte Forman*, 230 USPQ 546 (BPAI 1986). Among these factors are: the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the breadth of the claims, the amount of direction or guidance present, and the presence or absence of working examples.

The claims are drawn to DNA sequences defined as the DNA inserts DR-B-A,DR-B-B, and DR-B-C, the expressed portion of these inserts and to DNA sequences which hybridize under "high criterium" to said sequences, as well as to DNA sequences that code for a portion of a polypeptide encoded by said DNA inserts, to DNA sequences complementary to said sequences and to DNA sequences which are recited as degenerate to any of said sequences. In further embodiments of the invention, DNA sequences are claimed which encode amino acid subsequences (8-14,26-32, 39-45,72-78) of the HLA Class II Beta chain locus and , portions of said sequences which are specific to a polymorphic region, complementary to said region, and to fragments of said sequences, or sequences degenerate to said sequences. DNA sequences

comprising sequences which encode amino acid sequences (8-14,26-32, 72-78) of the HLA Class II Beta chain locus are recited as are fragments of said sequences. Methods of typing HLA molecules using said sequences are claimed as well as a process for producing a DNA sequence or polypeptide by transforminng host cells with said sequences.

The claims encompass a diverse number of DNA sequences that are defined by the limitation of hybridization under "high criterium" to said DNA sequences , by the limitation of DNA sequences that "encode polypeptides encoded by such sequences", and by the limitation of sequences which are "degenerate" to any of the sequences claimed. Claims drawn to DNA sequences comprising sequences which encode amino acid sequences (8-14,26-32, 72-78) of the HLA Class II Beta chain l encompass sequences encoding many additional amino acids in addition to (8-14,26-32, 72-78) and fragments of said sequences encompass DNA sequences of an unspecified number of bases which do not necessarily encode amino acids 8-14,26-32,or 72-78 .

The art at the time of the time that the invention was made had only begun to assess parameters required to determine the specificity of hybridization of DNA probes. Wallace and Sambrook in 1987, taught that determining the specificity of hybridization probes is empirical by nature and that the determining the specificity of hybridization probes is unpredictable. The art at the time that the invention was made did not teach how one could predictably design degenerate sequences for use as probes . The art further does not now recognize that sequences encoding unspecified portions of amino acids" embedded in sequences of undefined composition may

posses properties such as specific hybridization or that the biological activity or antigenicity of proteins or peptides encoded by such sequences might be predicted.

The specification teaches the sequences or the inserts DR-B-A , DR-B-B, and DR-B-C and subsequences within theses sequences which are the sites of polymorphisms (i.e useful for HLA typing) . However the specification does not teach or provide guidance to allow one to determine the composition of the diverse sequences claimed which hybridize under high criteria, code for undefined portions of of polypeptides and does not teach how one might use fragments of undefined length of such sequences or which comprise degenerate sequences to these sequences (it is not clear even what the metes and bounds of degenerate sequences are in the context of the claims). In failing to provide such guidance it would require a trial and error process for one of ordinary skill in the art to determine sequences which have the stated utility disclosed in the specification- to serve as hybridization probes useful for HLA-typing or as sources of recombinant proteins which are antigenic. It is therefore the position of the examiner, that in view of the unpredictability of the art, and the lack of guidance provided in the specification that it would require undue experimentation for one of skill and the art to make and use the products, and to perform the methods of the claims as broadly written.

2. Claims 23,24, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

Claim 23 is indefinite in step c in that it is not clear what the recitation of "high criterium" refers to (high stringency?). (see all claims for examples of this language)

Claim 23 is indefinite in the recitation of "DNA sequences which as a result of the genetic code are degenerate to" as it is not clear "what degenerate to " means . The claim might be amended to recite --DNA sequences which differ from the foregoing sequences in codon sequence due to degeneracy of the genetic code--

Claim 31, for example, is indefinite in the recitation of "degenerate to" as discussed above.

3 4. Claims 16, 41,42,44 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2173.05(l). The omitted steps are: a step which completes the preamble of the claim, i.e a

comparing step by which the results of the hybridization are actually used to determine an HLA-type .

Double Patenting

4 7. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16, 17,20,22-47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 5169941. Although the conflicting claims are not identical, they are not patentably distinct from each other.

a.The claims of the instant application differ from those of USPAT 5169941 in claiming sequences by virtue of their hybridization properties or claiming degenerate sequences, and

further in claiming specific polymorphic regions of these sequences or specific sequences to be used as hybridization control sequences. A subset of claims further recite a process of HLA typing using these sequences and processes of producing proteins expressed by these sequences. This subject matter is encompassed by the claims of the '941 patent which claims sequences that are selected from the DNA inserts DR B-A, DR-B-B, and DR-B-B, (i.e said sequences inherently posses the property of specific hybridization under conditions of "high criterium", to sequences "consisting essentially of said sequences" (encompassing degenerate sequences") and to fragments of portions of said sequences. The claims of the '941 patent to not recite specific amino acid sequences to be encoded by such sequences but the claims of the instant application directed to particular amino acid sequences also recite "portions", sequences complementary to said sequences" (i.e encompassing sequences that are only partially complementary to said sequences), sequences degenerate to said sequences and sequences comprisiing said sequences and therefore are not distinguished over the claims of the '941 patent.

Response to Applicant's arguments:

The rejection of claims under 35 USC 112 first paragraph.

Applicant argues by virtue of the specific disclosure of DNA sequences by Applicant of DR-B-A and DR-B-B, applicants have enabled portions of these sequences which hybridize to them, as well as nucleotide sequences which, due to the degeneracy of the genetic code code for the same polypeptides as those encoded by each specific sequence. Applicant argues that with Applicants' disclosure, one of skill in the art would appreciate that the useful DNA sequences are those that selectively hybridize and that it would be routine for one of skill in the art to determine the length of a DNA sequence that will specifically hybridize to a particular sequence in the human genome. Applicant argues further that they have taught DNA fragments which are identical to those disclosed and those which comprise mismatches. Fragments with mismatches will hybridize only to an individual having a particular HLA-DR type. Applicant further argues that they have identified polymorphic regions and conserved regions and that it would be routine for one of ordinary skill int he art to sequence applicants DR-B-C or DR-B-D DNA inserts and compare their sequences to each other or to the sequences of DR-B -A or DR-B-B. By comparing the sequences one of ordinary skill could identify specific regions of mismatch that would code for amino acid mismatches. Applicant further recites a passage from Sambrook et al which states that hybridization specificity of oligoncleotide probes allows one to screen for genomic clones or cDNAs, to screen for new alleles, to screen for specific mutants or to screen libraries with probes.

It is noted that all questions of enablement are evaluated against the claimed subject matter. As stated *in Vaek* (CAFC) 20 USPQ2d 1438, the "specification must teach those of skill

in the art how to make and how to use the invention as broadly as it is claimed." The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art . *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) Very recently, the Court has held in *Genentech Inc. v Novo Nordisk A/S CAFC No. 96-1440, 3/17/97* that "It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement" and further "Where as here, the claimed invention is the application of an unpredictable technology in the early stages of development, an enabling description in the specification must provide those skilled in the art with a specific and useful teaching".

The main issues of concern to the Examiner in the rejection made are that the methods recited never clearly recite the slectivity or specificity of hybridization. The use of the term "high criterium" as discussed above , is ambiguous and not one standardly used by those of skill in the art. If applicant amendes the claim as suggested above to define high criterium, than this aspect of the rejection would be overcome (see,for example, as done in claim 31). Applicant's argument that one of skill in the art would appreciate that the useful DNA sequences are those that selectively hybridize, and that it would be routine for one of skill in the art tp determine the length of a DNA sequence that will specifically hybridize to a particular sequence in the human genome is not persuasive since the claims are not limited to methods using sequences which specifically hybridize, but those which hybridize under high criterium or fragments of particular recited sequences. With regards to claims directed to fragments there is no recitation of either a minimum

size fragment or the functional properties of the fragment ; the claims encompass a large genus of fragments which are not useful as well as those which might be. In the instant case, given the large genus recited one cannot simply select from the genus claimed to arrive at those fragments which will work. Fragments under 6 bases for example will hybridize inefficiently to any sequences (yet these are encompassed by the claims) fragments much larger than 50 bases will not be able to hybridize but not be able to predictably serve as allele specific oligonucleotides (these too are encompassed by the claim). Therefore the teachings of the specification are not commensurate with the breadth of the claims. This aspect of the rejection may be overcome by reciting with more particularity the nature of the fragments.

It is unclear how Sambrook is relied upon in Applicant's response. The particular passage cited merely states that probes can hybridize to a variety of different types of DNA , but makes no mention of specificity and provides no teaching of probes that hybridize to one particular allele and not another when two alleles are present as is required for an HLA typing method.

Rejection of claims under 112 second paragraph.

The rejection of claims under 35 USC 112 second paragraph is withdrawn in part and maintained in part. Applicant's amendments have necessitated a new grounds of rejection under 35 USC 112 second paragraph.\

The rejection of the claims over the use of the term "high criterium" is maintained as indefinite.

Applicant argues that the specification defines "high criterium as 5°C below Tm. This point is taken ,however those of skill in the art define hybridization conditions in a multitude of different ways and as the limitations of the specification may not be read into the claims , the claims should be amended to include the recitation of 5oC below Tm.

The rejection of claims under 112 second paragraph as being incomplete for omitting essential steps is maintained.

Applicant argues that the patentability of Applicant's HLA-DR typing process is based on the discovery that the recited sequences allows one on to determine the HLA-DR specificity and that this is independent of steps relating ares of hybridization between the sample and the particular DNA sequence to areas pf hybridization between DNA of one HLA -DR type and that DNA sequence.

This argument is considered but is not deemed persuasive.

The claims are drawn to HLA-typing processes. The outcome of the process must therefore be that HLA typing is accomplished. HLA typing is not simply determining hybridization but assessing what a particular hybridization pattern means . The claims nowehere recite that after hybridization, one actually determines HLA-DR specificity (Applicant's argued patentable feature); therefore, the methods as recited are incomplete.

The rejection of claims under 35 USC 101 is withdrawn in view of Applicant's amendment to recite "isolated ". However, it is noted that in Applicant's response it is stated that "Applicant's

have obviated the rejection by amendment so that the claims incorporate the phrase 'essentially free of contaminating HLA-DR factors and other proteins of human origin". The Examiner notes that this amendment was not made to the claims and is unclear if this was intended by Applicant.

Double patenting rejections

Applicant argues that they will file a Terminal Disclaimer upon the Examiner's indication of allowable subject matter. The rejection is therefore maintained as not specifically traversed by Applicant.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Official Communications are (703) 305-3014 and (703) 305-4227. Please note that the faxing of such papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989). Applicant is informed that all Official communications that go through the Fax Center will not be forwarded directly to the Examiner but will be routed through docketing. Applicant is encouraged to clearly mark any communications to the Office as DRAFT, OFFICIAL (and further as RESPONSE TO OFFICE ACTION, or AFTER FINAL. etc.) For any inquiries concerning the status of of a Faxed Communication please contact (703) 308-9378.

An inquiry regarding the Office Action should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703) 308-6565. If Applicant does not receive a complete office action or references, please contact Donna Chapman , whose telephone number is (703) 308-3081. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Calls of a general nature may be directed to the Group receptionist who may be reached at (703) 308-0196.

Dianne Rees

Dianne Rees

7/19/97

W. GARY JONES
SUPERVISORY PATENT EXAMINER
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7/21/97